Treatment of aggressive lymphoma

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Treatment of aggressive B cell lymphomas is rapidly evolving with the introduction of monoclonal antibodies in association with chemotherapy. Reappraisal of the progress made with chemotherapy is important to decide which part of the past strategies with intensive treatment should still be used. Long term results of the first studies with R-CHOP, identify patients more likely to respond to treatment with Bcl2 over expression and low-intermediate risk factors. However, poor prognosis patients still exist and remain a challenge for investigations. Improving the use of chemotherapy and monoclonal antibodies will be the goals of the design of prospective studies.

Aggressive lymphomas are identified in the WHO classification[1] which will evolve with molecular biology findings. Before rituximab, several attempts were made in randomized studies to improve the results of the gold standard CHOP chemotherapy regimen with limited success. The introduction of monoclonal antibodies such as Rituximab had changed the approach of treatment B cell lymphoma patients. Revisiting the progress made before rituximab era is important to improve and understand the results of the combination of chemotherapy and monoclonal antibodies. Stratification of patients according to clinical prognostic factors of the international prognostic index (IPI) has been for a long time efficient in tailoring therapy and in comparing different trials. However the definition of poor prognosis lymphoma will be soon further described with novel bio-markers and more targeted treatment will emerge from this research work.

First line treatment

The results of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) established this regimen as a standard for several decades. However, with a projected disease free survival rate of 36%, it is not an ideal treatment and there is a need for better treatment approaches especially in poor prognosis Lymphoma. In the early eighties our group, GELA, was already convinced that it was possible to improve the results of CHOP and run several phases II and randomized studies with dose intensive regimens. This question was successively addressed in the different subgroups defined by the IPI and histological subtypes of B or T cell lymphomas. The innovative dose intensive regimen ACVBP was first used in all different types of aggressive lymphomas[2] in a large one arm study LNH 84. Then it was used as control arm in subsequent randomized studies.

Progress in the treatment before Rituximab.

Three European randomized studies based on more intensive chemotherapy demonstrated before Rituximab era the superiority of intensive chemotherapy when compared to CHOP. The first comparison was made against m-BACOD, a superiority of ACVBP was observed in a subset of patients with high LDH level or disseminated stages. Because published series appear heterogeneous with regard to prognostic factors, we conducted a new randomized trial in which we compared the ACVBP chemotherapy regimen with standard CHOP.[3] Patients 61 to 69 years of age who had aggressive non-Hodgkin's lymphoma with at least one adverse prognostic factor (advanced stage, poor performance status or elevated LDH level) were randomly assigned to receive ACVBP or standard CHOP. Of the 635 patients eligible; the rate of complete response was 58 percent in the ACVBP group and 56 percent in the CHOP group (p=0.5). Treatment related death occurred in 13 percent of the ACVBP group and 7 percent of the CHOP group (p=0.014). At three years, the event-free survival was 45 percent (95 percent confidence interval, 0.40 to 0.51) in the ACVBP group and 33 percent (95 percent confidence interval, 0.28 to 0.39) in the CHOP group (p=0.004). The disease-free survival at three years was better in the ACVBP group (p=0.0003). The difference in overall survival was in favour of the ACVBP arm mostly in patients under

65 years. The conclusion was that ACVBP is a more toxic regimen than CHOP but it prolongs survival and event-free survival in patients with poor-risk aggressive lymphoma. It should be restricted to patients in good performance status and under the age of 65 yr. The CR rate was still insufficient.

More recently,[4] dose intensification was made by shortening the interval between cycles and to determine whether biweekly CHOP (CHOP-14) with or without etoposide was more effective than CHOP-21. 689 patients ages 61 to 75 years were randomized to 6 cycles of CHOP-21, CHOP-14, CHOEP-21 (CHOP plus etoposide 100 mg/m^2 days 1-3), or CHOEP-14. Complete remission rates were 60.1% (CHOP-21), 70.0% (CHOEP-21), 76.1% (CHOP-14), and 71.6% (CHOEP-14). Five-year event-free and overall survival rates were 32.5% and 40.6%, respectively, for CHOP-21 and 43.8% and 53.3%, respectively, for CHOP-14. In a multivariate analysis, the relative risk reduction was 0.66 ($P \geq 0.003$) for event-free and 0.58 ($p < 0.001$) for overall survival after CHOP-14 compared with CHOP-21. Toxicity of CHOP-14 and CHOP-21 was similar, but CHOEP-21 and in particular CHOEP-14 were more toxic. Due to its favorable efficacy and toxicity profile, CHOP-14 was proposed as a new standard chemotherapy regimen for patients ages 60 or older with aggressive lymphoma.

Progress in the treatment with Rituximab

Rituximab, a chimeric anti-CD20 IgG1 monoclonal antibody, is effective when given as a single agent in the treatment of relapsed or refractory indolent lymphomas and has activity in relapsed or refractory diffuse large-B-cell lymphoma. The GELA undertook a study to compare CHOP plus rituximab with CHOP alone in elderly patients with diffuse large-B-cell lymphoma.[5] Previously untreated patients with diffuse large-B-cell lymphoma, 60 to 80 years old, were randomly assigned to receive either eight cycles of CHOP every three weeks (197 patients) or eight cycles of CHOP plus rituximab given on day 1 of each cycle (202 patients). The rate of complete response was significantly higher in the group that received CHOP plus rituximab than in the group that received CHOP alone (76 percent vs. 63 percent, p=0.005). Event-free and overall survival times were significantly higher in the CHOP-plus rituximab group (p<0.001 and p=0.007, respectively). The addition of rituximab to standard CHOP chemotherapy significantly reduced the risk of treatment failure and death. Rituximab plus CHOP overcomes bcl-2-associated adverse prognostic factor on overall survival in 292 elderly patients with diffuse large B-cell lymphoma (DLBCL).[6] Updated results with a 5-year median follow-up confirm this benefit on Overall survival 59% vs 48%. Deaths during the first two years mostly reflect resistance to chemotherapy. In the other hand, in this study population aged 60-80 yrs, delayed deaths could be due to the return of the underlying mortality hazard (e.g. age-associated morbidity such as cardio-vascular event).[7]

Within this framework, the information regarding the long-term impact of bcl-2 expression is scarce and does not take into account the presence of competing risks between death, relapse and age-associated morbidity. Results of the multivariate analysis demonstrated that lymphoma-related factors like the aa-IPI had no predictive value in Bcl2 negative patients. Moreover in this subgroup of good prognostic patients, the age plays a major role to predict the probability of death. On the other hand, in bcl-2-positive patients, the age had no prognostic value and lymphoma related factors are highly significant. On particular interest, rituximab significantly decreases the risk of progression or relapse in both bcl-2-positive and bcl-2 negative with a larger impact in bcl-2-positive patients (RR=2.18 vs 2.57).

Rituximab has been shown to improve outcome in elderly patients with DLBCL but there was only limited data for young low-risk patients. An intergroup study (MINT) was conducted in 18 countries[8] for younger untreated patients (18-60 years) with low-risk CD20+ DLBCL (IPI 0 or 1, stages II-IV and stage I with bulk). After a median time of observation of 22 months, R-CHEMO patients had a significantly longer TTF (p<0.00001), with estimated 2-year TTF rates of 60% (CHEMO) vs 76% (R-CHEMO). Complete remission (CR) rates of evaluable patients (CR) were significantly different (67% CHEMO vs 81% R-CHEMO, p<0.0001) as were the rates of progressive disease during treatment (15% vs 4%, p<0.00001). Similarly, overall survival was significantly different (p<0.001), with 2-year survival rates of 87% (CHEMO) and 94% (R-CHEMO), respectively.

R-CHOP is now a recognized standard of treatment.

The best effect of rituximab is seen in patients with 0-1 IPI factors and those overexpressing Bcl2 oncoprotein.[7] Although, major progress have been made since the introduction of Rituximab in the armentarium of treatment of lymphoma, progress should continue for poor prognosis patients as results are far from being satisfactory, and lessons coming from stem cell transplantation should be revaluated.

Autologous stem cell transplantation

High dose therapy (HDT) with autologous stem cell transplantation (ASCT) has the potential to increase cure rates of chemosensitive disease that displays a steep dose-response curve. It has a significant survival advantage over conventional treatment for those with relapsed disease. What is not clear is whether HDT

should be used up-front as part of first-line therapy in patients with poor prognoses, or should be withheld until these patients relapse. However, less than 40% of relapsing patients will be transplanted, mainly due to a lack of chemosensitivity. Then, one of the greatest challenges is to identify those patients who are unlikely to respond to standard therapy or whose response will be of short duration. Many prognostic factors have now been standardized, while studies are progressing in the identification of new factors, such as the molecular markers. The IPI appears to be robust when compared to other indices. However, the parameters corresponding to an increased risk of relapse are also associated with a decreased likelihood of obtaining complete remission. Several investigators have reported their findings on the use of HDT as consolidation therapy for poor-prognostic patients.

Most of the data suggest prolonged survival for HDT over controls or historical comparisons. Four randomized trials provide positive information on the role of HDT in patients with adverse prognostic factors. In the GELA, LNH87-2 study, 1043 patients with various adverse prognostic factors were enrolled.[9] Complete remission was achieved in 614 patients, who were then randomized to receive either intensive consolidation with HDT or sequential chemotherapy. There was no difference in overall survival or disease-free survival between the two consolidation arms. However, for the subgroup of 236 patients with at least two adverse IPI factors, HDT had a significant advantage in terms of 8-year disease-free survival (55% vs. 39%, p=0.01) and in survival (64% vs. 39% respectively, p=0.04)

Recently[10] was reported a randomized study comparing high-dose therapy plus autologous stem-cell support with the standard regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Of 207 consecutive patients, 197 underwent randomization; 99 were assigned to receive CHOP, and 98 to receive high-dose chemotherapy plus stem-cell transplantation. Overall, 78 percent of the patients completed the assigned treatment; the median follow up was four years. The estimated event-free survival rate at five years was significantly higher among patients who received high-dose therapy than among patients who received CHOP (55±5 percent vs. 37±5 percent, p=0.037). Among patients with 2 AaIPI factors the five-year survival rate was significantly higher after high-dose therapy than after CHOP (74±6 percent vs. 44±7 percent, p=0.001).

However, several other studies with different design and patients selection were not able to confirm these results. The absence of consensus on prognostic factors for patient treated with consolidate ASCT increases the difficulty to compare studies or to design clinical trials on maintenance therapy. We aimed to estimate the prognostic effect of clinical and biological variables by pooling the data from GELA trials on up-front ASCT.[11]

330 CR patients less than 60 years received ASCT after induction ACBVP regimen as in the LNH 87 study. Aa-IPI score was equal to 0 in 11%; 1 in 23%, 2 in 51% and 3 in 15%. 140 pts (43%) had more than one extranodal site and 69 pts had marrow involvement. The histological distribution showed: B aggressive NHL in 249 pts (75%), T NHL in 52 pts (including 23 T anaplastic) and non classified NHL in 29 pts. With a median follow-up of 6.5 yrs range [0.5; 12.1], the 5yr OS was 75±5% and EFS 67±5%. The univariate analysis showed that aa-IPI (0-1 vs. 2-3) had no prognostic value (5yr OS 76 vs 74%,p=0.48; EFS 65 vs 66%, p= 0.67) and only the following parameters had a significant (p<0.05) adverse effect: age>35 years old, marrow involvement, no of extra-nodal sites >1, type of anthracyclin (mitoxantrone vs. doxorubicin), anthracycline dose-intensity below 85%, cyclophosphamide dose-intensity below 85% and histology (non Anaplastic T vs others).

A complementary pair-matched analysis from the same GELA data base (on histology, phenotype, extranodal sites, marrow and anthracycline) with control patients treated with ACVBP induction and sequential consolidation chemotherapy confirmed the poor prognosis of non anaplastic T NHL (5 years OS=44% (chemo) vs 49% (ASCT) p=0.87, EFS=38% vs 45% p=0.89), but the high efficacy of up front ASCT in responding B cell lymphoma patients. Our results suggest that ASCT is able to prevent chemotherapy failure in patients with adverse aa-IPI factors. However, patients presenting with T phenotype or more than one extranodal site have still a higher risk of relapse.

Which directions?

It should again be pointed out that the results obtained for poor prognosis patients are not satisfactory with R-CHOP or with ACVBP. Improving the CR rate remains the major goal for these high risk patients. Incorporating new agents such, as anti-CD 20 might be the easiest way to improve the results obtained with chemotherapy followed or not by consolidation with HDT, and are presently under investigation. But, it is not known if the addition of Rituximab in more intensive regimen for poor prognosis lymphoma will increase the CR rate. Some new prognostic factors are coming which may select groups of patient for more tailored treatment. Some insights in the studies provide important information. The superiority of CHOEP over CHOP was neutralized in all subgroups of patients with good prognoses treated in the Mint study. The long term results of the R-CHOP regimen did not shown a significant advantage in survival

for elderly patients with poor prognoses. The other use of rituximab could be as maintenance post transplantation in order to reduce the relapse rate. Encouraging data were provided in low grade lymphoma and is under study in high grade lymphoma From these experiences, it is clear that NHL remain sensitive to chemotherapy after relapses. However, the duration of response will depend not only on the quality of salvage regimen but on several factors: time to relapse, on/off therapy, prior treatment, stage. Results should be interpreted with these parameters. In NHL large prospective studies with new combination chemotherapy with rituximab are necessary to establish some standard for salvage chemotherapy. What is clear from the available data is that patients who are not in complete remission at the beginning of the preparative regimen fare less well than those who have responded to conventional chemotherapy and are disease free (or nearly so) at that time. Furthermore, it is now evident that the procedure is not indicated for patients who have disease refractory to conventional salvage treatment. It is still unclear whether variations of the standard preparative regimen or bone-marrow purging can have a significant impact on outcome. Recently several alternatives such as tandem transplants or early transplant have been explored without success by our group. Radio labelled monoclonal antibodies (Bexxar or Zevalin) have been introduced in conditioning regimen and with significant improvement when compared to historical control has been reported. There is no doubt that monoclonal antibodies integrated in the strategies of ASCT will open for the coming years new opportunities of improving the cure rate of lymphomas.

References

1. Harris N. World Health Organization Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid tissues: Report of the Clinical Advisory Committee Meeting-Airlie House, Virginia, November 1997. J Clin Oncol 1999;17: 3835-49.
2. Coiffier B, Gisselbrecht C, Herbrecht R, et al. LNH84 regimen: a multicenter study of intensive chemotherapy in 737 patients with aggressive malignant lymphoma. J Clin Oncol 1989;7:1018-26.
3. Tilly H, Lepage E, Coiffier B, et al. Intensive conventional chemotherapy (ACVPB regimen) compared with standard CHOP for poor-prognosis aggressive non-Hodgkin's lymphoma. Blood 2003; 102: 4284-89.
4. Pfreundschuh M, Trümper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood 2004;104:634-41.
5. Coiffier B, Lepage E, Brière J, et al. CHOP plus Rituximab with CHOP chemotherapy in elderly patients with diffuse large B-cell lymphoma. A Groupe d'Etude des Lymphomes de l'Adulte study. N Engl J Med 2002;346:235-42.
6. N Mounier, J Brière, C Gisselbrecht, et al. For the Groupe d'Etude des Lymphomes de l'Adulte. Rituximab plus CHOP (R-CHOP) in the treatment of elderly patients with diffuse large B-cell lymphome (DLBCL) overcomes Bcl2 associated chemotherapy resistance. Blood 2003;101:4279-84.
7. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol. 2005;23:4117-4126.
8. Pfreundschuh M, Truemper L, Gill D, et al. First analysis of the completed Mabthera international (MinT) trial in young patients with low-risk diffuse large B-cell lymphoma (DLBCL): Addition of Rituximab to a CHOP-like regimen significantly improves outcome of all patients with the identification of a very favourable subgroup with IPI=0 and no bulky disease. Blood 2004; 104:abstract 157.
9. Haioun C, Lepage E, Gisselbrecht C, et al. Survival benefit of high dose therapy in poor risk aggressive non-hodgkin's lymphoma: final analysis of the prospective LNH87-2 protocol – A Groupe d'Etude des Lymphomes de l'Adulte study. J Clin Oncol 2000;18:3025-30.
10. Milpied N Deconinck E, Gaillard F, et al. Initial treatment of aggressive lymphoma with high-dose chemotherapy and autologous stem cell support. N Engl J Med 2004; 350:1287-95.
11. Mounier N, Gisselbrecht C, Brière J, et al. Prognostic factors in patients with aggressive non-hodgkin's lymphoma treated by front-line autotransplantation after complete remission: a cohort study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2004;22:2826-34.